Plasma Norepinephrine Kinetics in Patients with Posttraumatic Stress Disorder

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To determine whether basal sympathetic nervous system (SNS) function is increased in patients with posttraumatic stress disorder (PTSD), we used a radioisotope dilution technique to assess basal arterialized plasma norepinephrine (NE) kinetics in 12 men who were Viet Nam combat veterans with PTSD and six normal controls. In addition to determining the rates of appearance of NE into, and clearance of NE from, plasma, we measured basal arterialized plasma levels of epinephrine (EPI), and also vital signs, in both groups. Patients with PTSD actually manifested lower arterialized plasma levels of NE, and had lower rates of appearance of NE into plasma, than did controls. The rate of NE clearance from plasma was unaltered in PTSD patients. Patients with PTSD also showed a trend toward lower arterialized EPI levels than controls, but manifested a trend toward higher diastolic blood pressure. Our data indicate that basal SNS activity is not increased in patients with PTSD and that previous reports of increased resting SNS activity in this population may instead reflect SNS reactivity.

Key words: Post-traumatic stress disorder, catecholamines, epinephrine, norepinephrine, sympathetic nervous system, stress

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Introduction

A significant body of data amassed over the past decade has suggested that patients with posttraumatic stress disorder (PTSD) may have increased basal levels of sympathetic nervous system (SNS) activity. Psychophysiological studies have reported increased resting heart rate in patients with PTSD compared with normal controls (Blanchard et al 1982; 1986; Gerardi et al 1989; Pallmeyer et al 1986; Pitman et al 1987) and compared with other patient groups (Pallmeyer et al 1986). Kosten et al (1987) reported higher 24-hour urinary catecholamines in hospitalized patients with PTSD than in other groups of inpatients. Yehuda et al (1994) have found higher 24-hour urinary dopamine (DA), norepinephrine (NE), and epinephrine (EPI) levels in unmedicated inpatients with PTSD than in normal controls, and higher 24-hour urinary excretion of DA and NE in holocaust survivors with PTSD compared to holocaust survivors without PTSD. Perry et al (1988) reported a decreased number of α_2-adrenergic receptor binding sites on platelets of PTSD patients, suggesting downregulation of these receptors secondary to increased circulating levels of NE and/or EPI in PTSD. Although these findings suggest

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that plasma levels of catecholamines may be elevated in PTSD, none of these studies was specifically designed to differentiate between basal, or tonic, and phasic elevations of plasma catecholamines. Either tonic or phasic increases in sympathoadrenal activity, or both, could have been responsible for the reported observations.

It is also important to note that one study (Pitman and Orr 1990) reported no difference in 24-hour urinary catecholamines between PTSD patients and trauma-exposed controls. In addition, a number of psychophysiological studies (Dobbs and Wilson 1960; see McFall et al 1989; Orr 1990 for review) have not found differences in basal vital signs in PTSD patients compared with controls. Due to the complexity of interactions among the regulatory and counterregulatory systems that determine their final values, heart rate and blood pressure are not the best indices of SNS activity. Moreover, many different factors, including the time subjects are allowed to achieve a basal state, can influence resting heart rate and blood pressure. Our group (McFall and Murburg 1994) has reviewed the methodologies used in the psychophysiological studies of patients with PTSD and found that studies using longer initial waiting periods prior to measuring basal vital signs were less likely to report differences between groups. We (McFall et al 1990) and others (Perry 1994) have reported that patients with PTSD take a longer time than controls to arrive at basal levels of vital signs and plasma catecholamines following stimulation. It is therefore possible that studies using initial waiting periods of too short duration might not be measuring true basal levels of SNS function in PTSD patients, but rather are detecting persistent SNS activation in response to a prior stimulus. Our own studies (McFall et al 1990, 1992) suggest that a waiting period of at least 30–60 min is needed for PTSD patients to achieve "baseline" autonomic and catecholamine levels, at least in certain situations. Using a 30-min premeasurement waiting period, we found no differences in basal heart rate, blood pressure, or levels of catecholamines in arterialized venous plasma in patients with PTSD compared with controls (McFall et al 1992).

The goal of the present study was to evaluate in a more accurate way basal SNS function in PTSD patients. To do so, we utilized a radioisotope dilution technique to assess NE kinetics in arterialized plasma. Plasma NE and EPI levels in plasma are determined not only by their rates of appearance into plasma but also by their rates of clearance, principally by neuronal reuptake (Best and Halter 1982; Esler et al 1979, 1988; Esler 1982, 1989). Thus, high plasma NE levels could reflect either increased NE appearance into, or reduced NE clearance from, plasma. The radioisotope dilution technique permits estimation of the rates of NE appearance and clearance, making it possible to determine whether increased plasma NE levels truly reflect increased output by sympathetic nerves or instead reflect a decrease in the rate of NE removal from plasma.

In addition, we once again measured vital signs, and the levels of NE and EPI in arterialized plasma, this time beginning measurements after a 90-min adaptation period to obviate the confound of delayed return to baseline following excitation. Our hypothesis was that PTSD patients would have increased resting levels of SNS activity, resulting in increased resting pulse rate and blood pressure, as well as increased rate of release of NE into plasma by sympathetic nerves and increased output of EPI by the adrenal medulla. As a result, basal plasma levels of NE and EPI and the rate of release of NE into plasma were expected to be increased in PTSD patients compared to normal controls. We further hypothesized that increased SNS activity would be correlated positively with intrusive symptoms of PTSD as measured by the Impact of Events Intrusion Subscale. Because previous studies of patients with major depression have described increased SNS activity, including increased rate of appearance of NE into plasma (Veith et al 1988, 1994), we also hypothesized that NE appearance rate might be correlated positively with patient scores on the Hamilton depression scale.

Methods and Materials

Subjects

PTSD subjects were 12 Vietnam veterans undergoing treatment for PTSD at the Veterans' Administration (VA) Medical Center or the Vietnam Veterans Outreach Center in Seattle. Ten patients were recruited from the inpatient psychiatry service, and the remaining two were outpatients. Eleven subjects were white and one was native Alaskan. The mean age for the PTSD subjects was 42.2 years. Control subjects ($n = 6$) were asymptomatic, nonpatient volunteers who responded to an advertisement to participate in the study for remuneration. All were white, and the average age of the group was 37.7 years. PTSD subjects' weight averaged 104% of ideal body weight, and controls averaged 107% of ideal body weight, as defined by the 1983 Metropolitan Life Insurance Tables. All subjects were physically healthy, having no diagnosable medical conditions. Participants abstained entirely from alcohol and illicit drug usage for at least 2 weeks, and had not taken psychotropic medications or other medications known to alter plasma catecholamine levels for at least 4 weeks prior to the study. All subjects except for one, who had undergone alcohol withdrawal treatment 6 weeks prior to participation, had been free of any substance dependence for over 1 year prior to study. Subjects habitually drank three or fewer cups of caffein-

Table 1. Psychometric Characteristics of PTSD Patients

Psychometric Scale	Mean ± SEM
Hamilton Depression Score	25.8 ± 2.37
Revised Combat Scale	8.9 ± 0.79
Mississippi Combat PTSD Scale	136.1 ± 3.6
Impact of Event Intrusion	28.4 ± 1.8
Impact of Event Avoidance	32.0 ± 1.4
Impact of Event Total	60.4 ± 1.9

ated beverages per day, and abstained completely from caffeine, nicotine, and food ingestion for 8 hours before the procedure began.

All subjects were screened using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 3rd ed, rev. (DSM-III-R) patient version (SCID) (Spitzer et al 1987). In order to be included in the study, PTSD subjects had to meet *DSM-III-R* criteria for PTSD by the SCID, while control subjects could not meet criteria for PTSD or any other mental disorder. PTSD patients also exceeded published scores for combat veterans diagnosed with PTSD on the Mississippi Scale for Combat-Related PTSD (possible range 0–175; cutoff 107) (Keane et al 1988), and the Impact of Event Scale (possible range 0–35 with mean score for Viet Nam combat veterans 25.6 for the Intrusion Subscale, and possible range 0–40 and mean score for Viet Nam combat veterans 27.7 for the Avoidance Subscale) (Zilberg et al 1982). Psychometric data for the PTSD group are shown in Table 1. Comorbid diagnoses for the PTSD sample were as follows: eight subjects had current major depression; one subject had dysthymia; two met criteria for both generalized anxiety disorder and panic disorder, but these anxiety syndromes were judged to be secondary to their PTSD; one been diagnosed with alcohol dependence in remission for 6 weeks; four had been diagnosed with alcohol dependence in remission for 1–7 years prior to study; four had histories of abusing other substances, in remission for 1–7 years prior to study. The average Hamilton Depression Rating Scale (23 item) score for the group was 26 (range, 14–40). Two patients, both of whom met criteria for current major depression, failed to show a suppression of their 4:00 PM plasma cortisol levels below 5 μg/dl following administration of dexamethasone 1 mg at 11:00 PM the night before; the remaining 10 showed suppression of cortisol levels in response to this dose of dexamethasone.

Procedure

The diagnostic interviews were administered to subjects within the week prior to the study day. Written informed consent was obtained at the time of interview.

Participants remained supine throughout the study. At 9 AM, each subject had an 18-gauge intravenous (iv) catheter placed in antecubital vein for infusion of [^{3}H]NE and a second 19-gauge intravenous catheter placed in a dorsal hand vein for blood sampling. The catheterized hand was then placed in a warming box at 60°C to arterialize the venous blood (Veith et al 1984). Normal saline containing 1000 U sodium heparin per 500 ml was infused at a rate sufficient to maintain patency of the catheter and to replace blood volume removed.

Subjects rested for 60 min after the intravenous catheter was determined to be operating. After this rest period subjects were given a 15 μCi/m^2 bolus injection of [^{3}H]NE (SA, 18.8–57.7 Ci/mmol; New England Nuclear, Boston, MA), followed by a constant infusion of [^{3}H]NE (0.35 μCi/m^2 × min; 0.013–0.030 nmol NE/min) administered using a syringe pump (Harvard Apparatus Co., South Natick, ME). Vital signs were determined and blood samples were obtained for measurement of plasma catecholamines and calculation of basal NE kinetics when the [^{3}H]NE infusion reached steady state (30, 40, and 50 minutes after injection of the bolus) (Veith et al, 1984). The [^{3}H]NE infusion was then stopped.

Analytical Methods

Plasma samples (10 ml) for NE and EPI were collected in prechilled glass tubes containing ethyleneglycol-bis-β-aminoethyl ether N,N^1-tetraacetic acid (EGTA) and reduced glutathione, and placed on ice until prompt centrifugation at 4°C. Plasma was then stored at −70°C until assay. Heart rate and blood pressure were measured using an automated ultrasonic detector (Dinamap, Criticon, Tampa, FL) calibrated to within 2 mmHg of a standard mercury column.

Circulating levels of NE and EPI were measured by single isotope enzymatic assay (Evans et al 1978) with duplicate determinations for each sample. The intraassay coefficient of variation for the plasma catecholamine assay in this laboratory is less than 5%; the interassay coefficient is 6.5% in the greater than 300 pg/ml range, and 12% in the 100 pg/ml range. [^{3}H]NE concentrations were determined by liquid scintillation counting of radiolabeled catecholamines in alumina-extracted plasma.

NE kinetics were determined using NE and [^{3}H]NE values from peripheral venous plasma that had been arterialized by warming the hand, as described above. This noninvasive method of approximating systemic plasma values has been used successfully to study the kinetics of a variety of substrates and hormones (Veith et al 1984; Abumrad et al 1981; McGuire et al 1976).

NE appearance and clearance rates were calculated according to the [^{3}H]NE dilution technique described by

Esler et al (1979). Using this method, known trace amounts of [^{3}H]NE are infused at a set rate. The extent to which the labeled NE is diluted by endogenously released NE allows estimation of the rate of NE appearance into plasma. Under steady-state conditions, the ratio of the labeled to unlabeled NE in the plasma is equal to the ratio of the labeled infusion rate and the endogenous appearance rate of NE. Since the infusion rate of labeled NE is known, and the concentrations of labeled and unlabeled NE can be measured, the appearance rate can be calculated:

$$\text{NE appearance rate} =$$

$$[^3\text{H}]\text{NE infusion rate} \times [\text{NE}]/[[^3\text{H}]\text{NE}]$$

At steady state, the rates of NE appearance into plasma and NE removal from plasma must be equal in order to maintain constant NE concentrations. Therefore, the clearance rate can be calculated by substituting the calculated NE appearance rate for the NE removal rate in the clearance equation:

$$\text{NE clearance rate} = \text{NE removal rate}/[\text{NE}]$$

The total tracer doses of [^{3}H]NE administered in this study comprise less than 1% of the resting NE levels in an average subject and so do not contribute significantly to circulating NE levels. The [^{3}H]NE infusion rate, which delivers 0.013–0.030 nmol NE/min, is 50 times smaller than an NE infusion rate previously shown to have no measurable effects on heart rate, blood pressure, or other metabolic parameters (Silverberg et al 1978). We have previously shown that more than 94% of the radioactivity recovered from plasma during the [^{3}H]NE infusion is present in the form of [^{3}H]NE, and the remainder is in the form of the two alumina-extractable metabolites, dihydroxyphenylglycol and dihydroxymandelic acid (Featherstone et al 1987). High specific activity triple-labeled ring [^{3}H]NE such as that used in this study has been shown previously not to produce a significant *in vivo* isotope effect on NE kinetics (Supiano et al 1990).

Statistical comparisons between the two groups were performed using Student's independent samples *t* test. Pearson correlations between NE appearance rate, which has been shown to be the most sensitive index of SNS activity utilized in this study (Veith et al 1984; Esler 1982), and the Hamilton D score on the one hand and the Intrusion subscale of the IES on the other were calculated and the probabilities corrected using the Bonferroni method. A Pearson correlation matrix was also calculated for diastolic blood pressure (DBP), NE appearance rate, and plasma NE. Again, probabilities were corrected using the Bonferroni method. A p value of <0.05 using a two-tailed t test was used as the cutoff for significance for all tests. Steady-state conditions were verified during baseline and postdrug [^{3}H]NE infusions by using ANOVA with repeated measures to test for differences in both [^{3}H]NE and NE levels among the three steady-state sampling points (30, 40, and 50 min after the start of the [^{3}H]NE infusion). All analyses were carried out using the Systat 5.12 program.

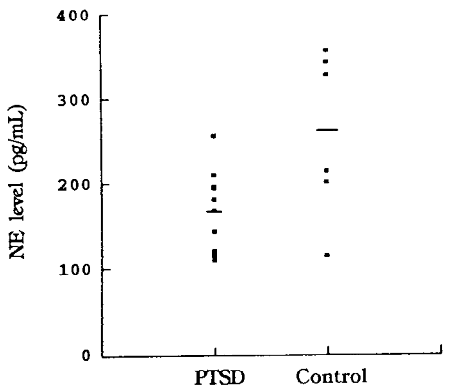

Figure 1. Patients with PTSD had a significantly lower mean level of NE (norepinephrine) in arterialized plasma than normal controls.

Results

The infusion was found to be at steady state in that there were no significant differences for the three values in [^{3}H]NE ($F = 1.898_{2,22}$; $p = 0.174$ for PTSD; $F = 1.160_{2,10}$; $p = 0.352$ for controls) or NE ($F = 0.1028_{2,22}$; $p = 0.903$ for PTSD; $F = 0.1429_{2,10}$; $p = 0.869$ for controls). Results in the text below indicate the mean ± standard deviation for each measurement. As shown in Figures 1 and 2, PTSD patients had lower plasma levels of NE (167 ± 47 vs. 259 ± 98 pg/ml; $p = 0.014$) and a trend towards lower plasma EPI (42 ± 28.4 vs. 68 ± 27.6

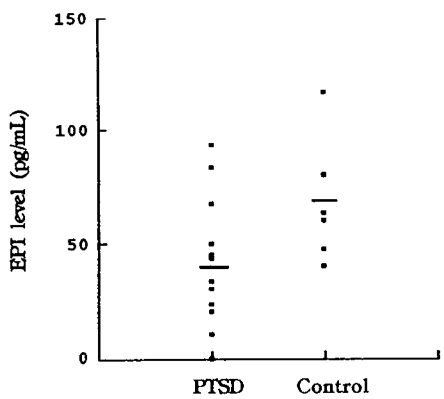

Figure 2. Patients with PTSD showed a trend toward a lower mean level of EPI (epinephrine) in arterialized plasma than normal controls.

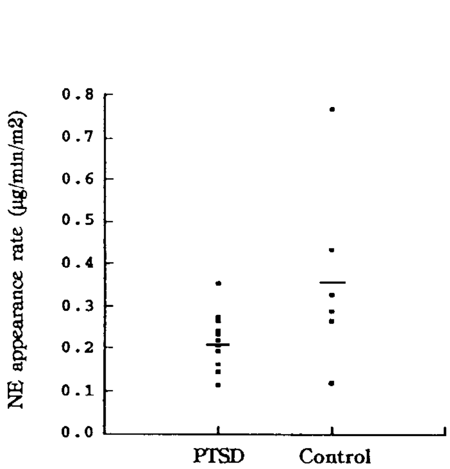

Figure 3. The mean rate of appearance of NE into plasma was significantly lower in PTSD patients than in controls.

pg/ml; $p = 0.080$), than controls. The lower levels of plasma NE in the PTSD subjects were due to a lower rate of appearance of NE into the plasma (0.213 ± 065 vs. 0.365 ± 0.220 μg/min/m^2; $p = 0.038$) (Figure 3), since the rates of clearance of NE from plasma were not significantly different for the two groups (1.267 ± 0.234 vs. 1.355 ± 0.415 L/min × m^2; $p = 0.568$). There were no significant differences in heart rate (HR) (64.5 ± 7.7 vs. 64.5 ± 9.23; $p = 0.983$) or systolic blood pressure (SBP) (119.2 ± 10.03 vs. 114.6 ± 8.2; $p = 0.349$) between PTSD subjects and controls. DBP showed a nonsignificant trend toward being higher in PTSD patients than in controls (78.6 ± 5.0 vs. 72.7 ± 8.1; $p = 0.076$). DBP was not correlated with NE appearance rate ($r = 0.418$; $p = 0.530$ for the PTSD group; $r = -0.132$; $p = 1.00$ for the control group) or plasma EPI level ($r = 0.599$; $p = 0.119$ for the PTSD group; $r = -0.164$; $p = 1.00$ for the control group) in either the PTSD or the control group. NE appearance rate was positively correlated with the intrusive subscale on the IES ($r = 0.6916$; $p = 0.038$) but not with the Hamilton depression score ($r = -0.4118$; $p = 0.551$)

Discussion

This is the first study of PTSD patients in which a radioisotope dilution technique has been utilized to measure the rates of appearance of NE into, and clearance of NE from, arterialized plasma. Our findings of lower basal NE and EPI plasma levels and of a lower rate of appearance of NE into plasma in PTSD patients contradicts the notion that basal SNS activity is elevated in PTSD, and suggests that, at least in the subject population studied under the experimental conditions of the current study, it is actually reduced. However, within the currently studied population of PTSD patients, those with higher scores on the Intrusion subscale of the IES had higher NE appearance rates. It is possible that the more symptomatic patients found the procedure more stressful and therefore exhibited a higher level of SNS activity, possibly reflecting some SNS excitation even under these experimental conditions, during the testing. Alternatively, traumatic stress exposure itself may have been responsible for nervous system changes that reduced basal SNS activity. The development and intensification of PTSD symptoms may have in part reversed this reduction, but clearly did not eliminate it. A three-way comparison among PTSD patients, trauma-exposed controls, and trauma-unexposed normal subjects would be necessary to determine which factor is responsible.

Our finding that basal HR and SBP in PTSD patients did not differ from controls in this study, which utilized a prolonged premeasurement waiting period, reinforces the need to give PTSD patients a sufficient opportunity to assume their true basal state prior to measuring SNS parameters. DBP was 6 mmHg higher in PTSD patients than in controls in this study, but our relatively small sample lacked statistical power to detect differences between groups in parameters such as blood pressure, in which the observed differences were likely to be small in magnitude. Thus, the DBP difference between groups was not statistically significant. As noted above there was no significant correlation between diastolic BP and NE appearance rate, or between DBP and plasma EPI in either PTSD patients or controls. This lack of correlation may again reflect the small sample sizes (for example, the correlation between DBP and plasma EPI in the PTSD group was 0.599, but this difference was not statistically significant using the relatively rigorous Bonferroni correction). However, the clear absence of a negative correlation between neuroendocrine indices of SNS function and DBP in the PTSD patients suggests that the apparent decrease in sympathetic nervous system activity in the PTSD patients was not due to a reflex response to an increase in DBP.

While our data may appear superficially to contradict some previous studies utilizing 24-hour urine collections to assess sympathetic nervous system function in PTSD patients, the methodologies employed address different questions. Measurement of catecholamines in 24-hour urine collections cannot address the question of differences in basal SNS activity between groups of subjects. Instead, such urinary measurements provide an indication of the net amount of unmetabolized catecholamines cleared by the kidney in response to both tonic and phasic release by the sympathoadrenal system over a 24-hour period. Furthermore, urinary excretion is responsible for the removal of only a small fraction of NE released from the SNS, with most NE released from sympathetic nerves being subject to removal by neuronal reuptake (Hoeldke et al 1983; Kopin 1985; Linares et al 1987). In contrast, measurement of catecholamine levels in arterialized plasma taken from calm, resting subjects whose diet, physical activity, and pharmacological status have been controlled, represents a net balance, at a particular time, between the rate of release of catecholamines into plasma by sympathetic nerves and the adrenal, and the rate of removal of catecholamines from plasma by neuronal reuptake and extraneuronal mechanisms. It has previously been shown that resting plasma NE levels correlate closely with direct measurements of peripheral sympathetic nerve activity in humans and that these measures are reproducible within individuals over periods of months to years (Wallin 1984).

Taken together, the existing data describing plasma and urinary catecholamines in PTSD suggest that PTSD patients experience phasic increases in sympathoadrenal activity that differentiate them from asymptomatic controls and from other psychiatric patient groups. These phasic increases in sympathoadrenal activity may be provoked by exposure of the patients to trauma-related stimuli. In contrast, the present study, together with our previous studies of basal sympathoadrenal function in PTSD patients (McFall et al 1992; Murburg et al 1994), suggest that basal SNS activity is similar or reduced in PTSD patients compared with normal controls. Even though eight of our patients displayed a syndrome meeting criteria for the diagnosis of comorbid major depression, PTSD patients in this study showed no evidence of the basal SNS hyperactivity typically seen in major depression (Veith et al 1994; Barnes et al 1983). It is interesting that the increase in plasma NE seen in major depression is most prominent in dexamethasone-resistant patients, and only two (both of whom met criteria for major depression) of our 12 PTSD patients failed to show suppression of their plasma cortisols below 5 μg/dl following administration of 1 mg dexamethasone. This low rate of dexamethasone nonsuppression in our PTSD group is not atypical of patients with PTSD, who have been found by Yehuda et al (1993) to exhibit not nonsuppression, but supersuppression, of cortisol in response to dexamethasone, even in doses as low as 0.5 mg, even in the subset of PTSD patients who also met criteria for concurrent major depression. Such differences in hypothalamus–pituitary–adrenal (HPA) axis and SNS activity between PTSD and major depression suggest that the syndrome of major depression seen as a comorbid complication of PTSD may differ in important biological aspects from primary major depression. Further studies are needed to clarify the biological differences between the syndromal depression complicating PTSD and primary major depression.

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